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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,324	04/19/2004	Bruce D. Weintraub	TROP-007/03US 304828-2020	1064

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,324	WEINTRAUB ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-221* is/are pending in the application.

4a) Of the above claim(s) *22-30,32-72,74-84 and 86-220* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,31,73,85 and 221* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *20-221* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

hanDETAILED ACTION

Election/Restrictions

In the previous Office Action it was stated:

Applicant's election without traverse of Invention I in the reply filed on 5/9/2007 is acknowledged.

Applicants election of the species N13B in the reply filed on 5/9/2007 is acknowledged. Applicants have requested (traversed) that the species N13Z also be examined, on the basis that a search for N13B would also reveal art as to the species N13Z. This argument is not strictly correct; different amino acids, with different charges, are being substituted, albeit at the same position. However, the Examiner will agree to examine N13Z as such does not at this time present an undue search burden.

Claims 20, 21, 31, 73 and 85 are under consideration. Claims 22-30, 32-72, 74-84 and 86-142 are withdrawn from prosecution as being drawn to a non-elected invention or species.

In response to the First Action on the Merits, applicants have amended claims 143-220 to depend from the previously elected claims. These claims are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: they require an additional mutation not required by the first elected invention, and would require not only a new species election, but a completely new search of the invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 143-220 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 20, 21, 31, 73, 85 and 222 are under consideration.

Priority

Priority for the claims under consideration remains set at 3/19/99.

Claim Interpretation

It is noted that applicants have amended the sequence listing, specifically SEQ ID NO: 3, to correspond to the art-accepted numbering.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20, 21, 31, 73 85, and 222 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is further indefinite as the metes and bounds of the claim cannot be determined because there is no indication of the upper limitation of mutations that may occur, including whether or not said mutations are limited to the recited portions of the molecule, and whether or not any structure and/or function must be maintained. Accordingly, one cannot be informed as to what molecules would or would not fall within the metes and bounds of the claims. At page 24 of the response, applicants argue that claim 20 is now definite because the function that "said mutation reasults in said hCG protein exhibiting increased hCG bioactivity, when read in light of the specification, obviates this rejection. This argument has been fully considered but is not deemed persuasive because (a) the claim is now essentially a single means claim, wherein at least one residue is required, and a single function is required, but other than that the remainder of the protein is not specified, and (b) limitations from the specification cannot be read into the claims. It remains that there is no upper limitation on the number of mutations that may occur, rendering the claims indefinite.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 21, 31, 73, 85 and 222 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hCGβ having mutation N13X (X being any amino acid, generically), does not reasonably provide enablement for hCGβ having an unspecified additional number of mutations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is the insertion of a mutation at a certain portion of the hCGβ molecule. The claims are extremely broad: There is no requirement for conservation of any activity. There is no requirement for possession of any activity. There is no upper limit on the number of mutations allowed, either in the specified region of the protein, or elsewhere. All that *is* required is that there be *at least* one electrostatic charge altering mutation in the specified region.

The state of the prior art is that hCGβ is well known in the art. Also, many mutations are known to have been made in hCGβ. However, the state of the prior art is also that it is not predictable what mutations will be tolerated in a protein such as hCGβ, especially considering that there is no upper limit on the number of changes encompassed by the claims. While many individual substitutions and even some multiple substitutions have been made in the art, it remains a very small number compared to the breadth of the claims.

The relative skill in the art is high with respect to the ability to generate mutated proteins. However, the relative skill in the art is low with respect to being able to predict the effects of said mutations. One illustrative piece of art is Campbell et al., WO91/16922, cited by applicants, wherein specific residues from the beta subunits of each glycoprotein hormone were substituted

into at least one of the other members of the family. However, those substitutions evince unpredictability, and do not even begin to address the scope of the pending claims.

It is noted that applicants have amended the claims to require increased bioactivity in the claimed protein. However, there is no specific guidance in the specification as to which species would have what properties. In fact, the specification at page 11 issues an invitation to experiment to determine what properties a molecule might have, stating:

> "The novel mutant CKGFs of the invention *alternatively possess*: (a) novel properties absent from naturally occurring or wild type CKGFs, or (b) improvements in desirable pharmacological properties that characterize wild type CKGFs. Preferably, when compared with wild type CKGFs, the novel mutant CKGFs disclosed herein have a higher affinity for their cognate receptors. Additionally, the novel mutant CKGFs can be either more active or less active in effecting receptor- mediated signal transduction. In certain embodiments, the novel mutant CKGFs have prolonged half-lives in vivo.
>
> The novel properties possessed by the mutant CKGF proteins arise from the amino acid substitutions, additions, or deletions that alter the electrostatic interactions that occur between the CKGF protein as ligand and its biological receptor. Positively charged residues in the peripheral loops of the CKGF proteins play an important role in receptor interaction. By altering the electrostatic nature of the peripheral loop common to the CKGF superfamily of proteins, mutant CKGF proteins are produced that display increased biological activity as compared to the wild type form of the molecule. Those proteins are one aspect of the present invention."

While hCG is discussed specifically at pages 73-76 of the specification, there is no guidance as to what the expected properties of the claimed muteins would be.

It is noted that the previous action erroneously stated that here are no working examples in the specification in which even a single mutein of hCG beta was made. The Examiner has now found such, specifically:

> [1216] In seventh and eighth experiments, two novel mutations in the .beta. hairpin L3 loop of the hCG-.beta. subunit, when expressed in combination with an .alpha.-subunit, increased the bioactivity of the resulting mutant hCG hormone. One mutation was a substitution of the glycine residue at position 75 with an arginine residue (hCG-.beta.G75R). The other mutation is a substitution of the asparagine residue at position 77 with an aspartate residue (hCG-.beta.N77D). Each of the mutant hCG .beta.-subunits was transiently expressed in CHO-K1 cells with a wild type common .alpha.-subunit to produce mutant hCG heterodimers. Each of the mutant hCG

heterodimers was then tested in a bioactivity assay using the murine Leydig cell line (MA-10) that produced progesterone following hCG stimulation. Both mutant hCG hormones induced higher levels of cAMP and progesterone production than did the wild type hCG. Substitution of asparagine 77 by aspartate in the human hCG .beta.-subunit (hCG-.beta.N77D) is the first example that introduction of negatively charged residues into the peripheral .beta. hairpin loops based on sequence alignments, and resulted in increased hormone binding and activity.

However, it remains that the working examples are not commensurate in scope with the claims, and that the elected species is not enabled.

While the person of ordinary skill in the art would know how to *make* species within the metes and bounds of the claims, the specification has not taught what properties such species would be expected to have. One would know how to use agonists or antagonists, but not species lacking activity. There is insufficient guidance to allow the person of ordinary skill in the art to predict in any manner what characteristics most of the encompassed species would have. There is no guidcance as to which species would be expected to result in increased progesterone production, other than the two exemplified in the paragraph above. Thus, given the breadth of the claims, the lack of working examples, and the unpredictability of the art, it remains that it would require undue experimentation to practice the claimed invention in a manner commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20, 73, 85 and 222 are rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as being obvious over Campbell et al., WO 91/16922, cited by applicants.

Campbell et al. teach muteins of glycoprotein hormones. A species having the substitution N13E (an acidic residue) is disclosed as species C1; see table III at page 62. This reference was cited under 35 U.S.C. §102(e) in the previous office action. In response, applicants have added a functional limitation, regarding which Campbell is silent.

The examiner is unable to determine whether the muteins of Campbell actually possesses the characteristic of increased biological activity. Under such circumstances, where the product seems to be identical, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of ***In re Best*** 195 USPQ 430, 433 (CCPA 1977).

Claims 20, 21, 31, 73 85 and 222 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moyle, U.S. Patent No. 7,001,597 in view of U.S. Patent No. 6486303 or U.S. Patent No. 5851997.

Moyle teaches muteins of hCG, which is produced in the form of a single chain gonadotropin. See Table 1, at column 44, which discloses numerous species with the mutation "N13X" in the hCG beta subunit. At column 45, lines 4-6, "N13X" is defines as "refers to the substitution of glutamine *or other amino acid* (emphasis added) for hCG β subunit residue asparagine 13 and analogs." Moyle teaches that such analogs are useful for various fertility-associated uses, see column 41, which discusses the expected properties of particular analogs.

Thus, Moyle teaches substitutions at N13, wherein the substitution may be any other amino acid. There are twenty naturally occurring, common amino acids. Thus, Moyle may be

fairly construed as teaching nineteen possible substitutions at N13. Of those nineteen, two are acidic and three are basic. Thus, 26% of the species suggested by Moyle fall within the metes and bounds of the claims.

It is well known in the art that administration of hCG increases progesterone production, and is used clinically in fertility treatments; see for example U.S. Patent No. 4006227 which teaches:

Detailed Description Text - DETX (67):
Following HCG administration there is a tendency to increase the plasma levels of progesterone on days 21, 22, and 23 as well as an increase of plasma levels of FSH and LH.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute any of the nineteen possible amino acids at the N13 position of hCGβ as taught by Moyle, with the reasonable expectation that they would be useful as taught by Moyle, and with a reasonable expectation that the activity of at least some of the muteins would be as good, or better, than wild-type hCG. Moyle discloses the position at which the substitution is to be made, and states that any amino acid may be substituted there. Thus, there is a finite number, 19, of predictable potential muteins disclosed by Moyle. The person of ordinary skill in the art would have pursued the known potential substitutions, without undue experimentation, and with a reasonable expectation of success. Further, in view of the two cited patents, the skilled artisan would recognize that a more potent form of the drug could be administered in smaller amounts, which is generally desirable. Accordingly, the claimed invention is *prima facie* obvious over Moyle in view of U.S. Patent No. 4006227.

The Examiner's position is supported by the recent finding by the Supreme Court in *KSR v. Teleflex, Inc.* (82 USPQ 2d 1385, 4/30/2007), which held that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." (See 82 USPQ2d at 1397.)

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/, Ph.D.
Primary Examiner